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Cardiovascular disease risk, awareness, and treatment in people with epilepsy



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ABSTRACT

Objective: To evaluate whether cardiovascular risk, risk awareness, and guideline concordant treatment differ in individuals with versus without epilepsy.

Methods: This was a retrospective cross-sectional study using the National Health and Nutrition Examination Survey. We included participants ≥ 18 years for 2013–2018. We classified participants as having epilepsy if reporting ≥ 1 medication treating seizures. We calculated 10-year atherosclerotic cardiovascular disease (ASCVD) risk using the revised pooled cohort equation. We compared unadjusted and adjusted risk for participants with versus without epilepsy. We then assessed hypertension and diabetes disease awareness and control, plus statin guideline-concordance. We assessed mediators for both ASCVD risk and cardiovascular disease awareness.

Results: Of 17,961 participants, 154 (0.9%) had epilepsy. Participants with epilepsy reported poorer diet ($p = 0.03$), fewer minutes of moderate-vigorous activity per day ($p < 0.01$), and increased frequency of cardiovascular conditions (e.g. coronary heart disease, myocardial infarction, stroke). There was no difference in control of individual examination and laboratory risk factors between groups (A1c, systolic blood pressure, diastolic blood pressure, high-density lipoprotein, low-density lipoprotein, total cholesterol). However, epilepsy was associated with 52% (95% confidence interval [CI]: 0–130%) increase in ASCVD risk, which became nonsignificant after adjusting for health behaviors. No single studied variable (income, Patient Health Questionnaire-9 (PHQ-9), diet, smoking) had a significant indirect effect. Participants with epilepsy reported increased hypertension awareness which was trivially but significantly mediated by having a routine place of healthcare (indirect effect: 1% absolute increase (95% CI: 0–1%), and they reported increased rates of hypertension treatment and guideline-concordant statin therapy. Participants with versus without epilepsy reported similar rates of blood pressure control and diabetes awareness, treatment, and control.

Conclusions: Participants with epilepsy had increased ASCVD risk, despite similar or better awareness, treatment, and control of individual risk factors such as diabetes and hypertension. Our results suggest that epilepsy is associated with numerous health behaviors leading to cardiovascular disease, though the causal pathway is complex as these variables (income, depression, diet, exercise, smoking) generally served as confounders rather than mediators.

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1. Introduction

While clinicians focus attention on sudden unexplained death in patients with epilepsy (SUDEP), large cohorts suggest that cardiovascular diseases cause up to 30–45% of deaths in people with epilepsy [1–10]. Fortunately, 30% of cardiovascular deaths are

thought to be preventable [11]. Thus, optimization of cardiovascular risk factors may provide substantial reduction in mortality and morbidity for people with epilepsy.

Previous cross-sectional surveys have documented increased rates of diabetes, coronary heart disease, hypertension, and stroke in patients with epilepsy [12–15]. However, such studies were limited by self-reported outcomes which could misclassify patients. Only limited literature has compared objective cardiovascular measurements in people with and without epilepsy [16], and no prior studies have compared aggregate cardiovascular risk. Furthermore, the causal pathway between epilepsy and cardiovascular disease is currently incompletely defined. For example, in the general population it has been documented that only ~50–70% of patients with hypertension or diabetes are actually aware of their diagnosis, and just 10–30% demonstrate risk factor control [17,18]. These issues may be even more problematic in epilepsy because of possible disparities in access or adherence [19]. Additional possible mediators between epilepsy and cardiovascular risk may include poorer health behaviors [20–22], lower socioeconomic status [19,23,24], or lipid-elevating enzyme-inducing antiseizure medications [25,26].

In this study, we leveraged a large nationally representative survey to compare aggregate calculated cardiovascular risk in people with versus without epilepsy. We performed serial modeling adjusting for a wide range of variables known to influence metabolic risk. We then compared risk factor awareness, guideline-concordant statin treatment, and risk factor control for people with versus without epilepsy. Finally, we performed mediation analysis to assess possible mechanisms underlying relationships between epilepsy and 10-year atherosclerotic cardiovascular disease (ASCVD) risk and/or cardiovascular risk awareness.

2. Methods

2.1. Study design and dataset

This was a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) using data collected from 2013–2018. NHANES is a long-standing semi-annual cross-sectional study run by the Centers for Disease Control and Prevention (<https://www.cdc.gov/nchs/nhanes/default.aspx>). Its goal is to understand broad trends in health and nutrition in the United States. NHANES samples 5000–10,000 non-institutionalized individuals from 15 counties across the US each year, and oversamples certain individuals (over 60 years old, African Americans, Hispanics) selected from the US Census to ensure it is nationally representative. It uses complex, stratified, multistage probability cluster sampling and collects data including respondents' prescribed medications and health conditions.

2.2. Procedures involving human subjects

This study was deemed exempt by the University of Michigan Institutional Review Board, given use of publicly available de-identified datasets.

2.3. Participant selection

We included participants at least 18 years old to focus on adults, and because NHANES does not collect information on smoking in younger participants. Smoking is required to calculate ASCVD risk. Note that while NHANES does inform the total number of ASMs taken by each participant, the dataset does not provide details regarding chronicity or refractoriness of epilepsy.

2.4. Variables

To identify epilepsy cases, we classified participants according to whether they responded they were taking at least one medication for epilepsy or seizures. Specifically, respondents were asked to list all medications prescribed by a healthcare professional which they have taken in the last 30 days, and provided up to 3 main reasons for using each medication. We confirmed that each medication with at least one listed reason being epilepsy or seizures was indeed a standard antiseizure medication (ASM). If a medication was reported for seizures but not actually an ASM by manual review, we did not count such medications toward our case definition. We further classified certain ASMs as enzyme-inducers (phenobarbital, phenytoin, carbamazepine, and primidone), as these have been associated with hyperlipidemia [25,26].

We collected baseline variables to describe our population. Demographics included age, sex, race, presence of health insurance, and income to poverty ratio (a family's income divided by regional poverty threshold). Given its potential relevance to disease awareness, we included two variables describing access/utilization of routine care: number of non-urgent healthcare encounters in the past year, and whether participants reported a routine place of non-urgent care. We included other general health conditions to describe our population including those related to cardiopulmonary functioning. Participants reported whether a doctor has ever told them they have a variety of conditions including asthma, cancer, chronic obstructive pulmonary disease, and thyroid disease. Participants also completed the Patient Health Questionnaire-9 (PHQ9) to evaluate depression at the time of the survey [27] which we include due to depression's relationship with the metabolic syndrome [28,29]. Other variables included overall self-rated health (5-point Likert scale: excellent to poor), body mass index (kg/m^2 ; both weight and height were taken from objective measurements by the NHANES examination team, not self-reported), and number of ASMs.

Information collected regarding cardiovascular risk factors consisted of behaviors, conditions, physical examination findings, and laboratory parameters. Behaviors included self-rated dietary healthfulness (5-point Likert scale: excellent to poor), minutes of moderate to vigorous work or recreational activity per day [30], current smoking, and alcoholic drinks per week. Cardiovascular conditions included whether each participant reported that a doctor had previously diagnosed them with hypertension, coronary heart disease, congestive heart failure, myocardial infarction, or stroke. Additionally, similar to what has been done in prior NHANES studies [17], participants were categorized as having hypertension or diabetes if (1) they reported taking at least one prescription medication for either condition, (2) they reported a physician had previously diagnosed them with the condition, or (3) NHANES measurements suggested the diagnosis (hypertension: of up to 3 readings, average systolic blood pressure (SBP) ≥ 140 mm Hg (≥ 130 mm Hg if diabetes) or average diastolic blood pressure (DBP) ≥ 90 mm Hg (≥ 80 mm Hg if diabetes); diabetes: A1c $\geq 6.5\%$ [31]). Additional laboratory risk factors included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) collected for those with a morning fasting blood draw, and total cholesterol. We calculated 10-year ASCVD risk (0–100%) for nonfatal myocardial infarction, death from coronary heart disease, or fatal or nonfatal stroke using the updated pooled cohort equation [32]. Variables and an example calculation are depicted in Supplemental table e-1.

We assessed cardiovascular risk factor awareness, treatment, and control as follows for hypertension and diabetes [17]. Awareness was defined as a participant reported that either (1) a doctor had previously diagnosed him/her with the condition, or (2) they reported at least one prescription medication for the condition.

Treatment was defined as taking at least one prescription medication for the condition (a subset of those classified as being aware of the condition). Control was defined according to standard guideline-driven recommendations as SBP <140 mm Hg (<130 mm Hg if diabetes) and DBP <90 mm Hg (<80 mm Hg if diabetes) [18] and A1c <7% [33]. Indications for a statin included clinical atherosclerotic disease [past myocardial infarction, stroke, or angina], diabetes, 10-year ASCVD risk \geq 7.5%, or LDL \geq 190 mg/dL [34,35]. Lipid guidelines released in 2013 endorsed targeting these 4 particular high-risk groups for statin therapy based on the pooled cohort equations released that year, rather than prior guidelines endorsing treatment primarily targeting LDL levels [36]. We used the updated guidelines in this study because our study population spans 2013–2018.

2.5. Statistical analyses

For categorical data, we reported raw counts and survey-weighted proportions. For normally distributed continuous data, we reported survey-weighted means plus standard deviations or 95% confidence intervals (CI). The weights provided in each biennial cycle's dataset were divided by 3 (the number of interview cycles we have used: 2013–2014, 2015–2016, 2017–2018), so that the estimates are nationally representative of the US population across the 6-year period [37].

We compared ASCVD risk between participants with and without epilepsy using survey-weighted linear regressions. We log-transformed ASCVD risks, as untransformed risk was right-skewed with heteroskedasticity across predictors and deciles of predicted ASCVD. Given the log-transformed outcome, we presented the percentage change in ASCVD risk for each 1-unit increase of each covariate, which was calculated as $(e^{\text{coefficient}} - 1) * 100\%$. Our analysis consisted of 4 serial models. Model 1 was unadjusted, only including the binary variable epilepsy. Model 2 was adjusted for relevant variables not included in ASCVD risk calculation: diet, activity, being on an enzyme-inducing ASM, body mass index (BMI), depression severity (PHQ-9), and stroke. Model 3 included Model 2's variables in addition to demographics (age, sex, and race) and smoking which are included in ASCVD risk calculation. We performed a fourth sensitivity analysis including all of Model 3's variables, in addition to family income to poverty ratio; this variable was added in a separate model due to more missing data in that variable. Missing data were handled by list-wise deletion.

We used survey-weighted chi-squared tests to compare awareness, treatment, and control for diabetes and hypertension. Denominators were either number of participants with the listed condition, or else number of participants with a statin indication, depending on the analysis. We also conducted sensitivity analyses where we modified the denominators as follows. First, we assessed

Table 1
Population description according to epilepsy status.

	Mean (SD; N) or Raw No./No. non-missing (weighted %) Epilepsy		p-value ^a
	Yes (N = 154)	No (N = 17,807)	
Demographics			
Age	48.6 (17.9; 154)	47.0 (17.7; 17,807)	0.43
Male sex	77/154 (54%)	8,566/17,807 (48%)	0.28
Race			0.61
	Mexican American	19/154 (7%)	2,685/17,807 (9%)
	Non-Hispanic black	31/154 (11%)	3,831/17,807 (11%)
	Non-Hispanic white	68/154 (67%)	6,449/17,807 (64%)
Uninsured	15/154 (10%)	3,217/17,766 (15%)	0.14
Number of non-urgent healthcare encounters in the last year	4.2 (2.4; 153)	2.4 (2.1; 17,775)	<0.01
Routine place for healthcare	144/154 (95%)	14,585/17,805 (83%)	<0.01
Family income to poverty ratio	2.1 (1.6; 141)	3.0 (1.7; 15,824)	<0.01
Conditions			
Number chronic conditions ^b	3.4 (2.4; 154)	1.4 (1.5; 17,807)	<0.01
Asthma	32/154 (22%)	2,707/17,791 (16%)	0.08
Chronic obstructive pulmonary disease	27/148 (20%)	1,453/16,889 (8%)	<0.01
Patient health questionnaire 9 (PHQ9) ^c	5.2 (5.8; 117)	3.2 (4.2; 15,539)	0.01
Thyroid disease	25/148 (22%)	1,853/16,853 (12%)	0.02
Self-rated health			
	Excellent	5/128 (6%)	1,372/15,664 (10%)
	Very good	15/128 (16%)	3,990/15,664 (31%)
	Good	43/128 (32%)	6,489/15,664 (40%)
	Fair	52/128 (38%)	3,274/15,664 (16%)
	Poor	13/128 (7%)	539/15,664 (2%)
Body mass index (kg/m²)	30.4 (9.0; 137)	29.4 (7.1; 16,806)	0.34
Medications^d			
Total number	5.6 (4.2; 154)	2.0 (2.8; 17,807)	<0.01
ASMs for epilepsy			N/A
	1	116 (73%)	N/A
	2	27 (18%)	
	3	7 (4%)	
	4	4 (4%)	
Inducing ASMs ^e	63/154 (38%)	34/17,807 (0.3%)	<0.01

^a p-values were calculated by survey-weighted Chi-squared tests for categorical variables and t-tests for continuous variables.

^b Number of chronic conditions equal the total number of conditions among epilepsy, asthma, chronic obstructive pulmonary disease, congestive heart failure, coronary disease, hypertension, diabetes, liver disease, thyroid disease, and malignancy.

^c Common interpretation thresholds for depression include 0–4 minimal, 5–9 mild, 10–14 moderate, 15–19 moderately severe, 20–27 severe [32].

^d Total number refers to the total number of prescription medications, which includes antiseizure medications (ASMs). ASMs refers to the total number of medications participants reported taking to treat seizures, which includes inducing ASMs. Inducing ASMs refers to phenobarbital, phenytoin, carbamazepine, and primidone, regardless of indication [21].

^e Inducing ASMs include phenobarbital, phenytoin, carbamazepine, and primidone.

awareness among those with measurements exceeding objective diagnostic thresholds (hypertension: SBP ≥ 140 (≥ 130 mm Hg if diabetes) or DBP ≥ 90 (≥ 80 mm Hg if diabetes); diabetes: A1c $\geq 6.5\%$), rather than in everyone with the condition as described above. We did this because self-report could misclassify participants for the denominator. Second, we assessed control among those aware of the condition, rather than in everyone with the condition. Third, we assessed awareness among those without prior clinical cardiovascular disease (coronary heart disease [CHD], myocardial infarction [MI], stroke), given awareness would be expected to be increased by secondary prevention efforts.

Finally, to explore mechanisms driving the relationship between epilepsy and the above outcomes (ASCVD risk, and disease awareness), we performed mediation analyses [38–41]. We did this because it is plausible that epilepsy may lead to downstream healthy behaviors (i.e. depression or more sedentary lifestyle) which themselves could lead to higher ASCVD risk (mediation), rather than less healthy behaviors themselves causing both epilepsy and ASCVD risk (confounding). We explain details in the Supplemental Methods appendix.

Data were analyzed using SAS 9.4 (Cary, NC), Stata 14.2 (College Station, TX), and RStudio version 4.0.1.

2.6. Data accessibility statement

All datasets are freely available for download at <https://www.cdc.gov/nchs/nhanes/Default.aspx>.

3. Results

3.1. Patient population

Our study included 17,961 participants. Of these, 154 (0.9%) were classified as having epilepsy. Supplemental table e-2 lists ASMs leading to classification as having epilepsy. Table 1 depicts participant characteristics for those with and without epilepsy. The population with epilepsy reported lower family income, a larger number of chronic conditions, worse PHQ-9 scores and self-rated health status, and a higher number of total medications. There were no significant differences between populations in age, sex, race, presence of health insurance, or BMI. Seventy-three percent of our population with epilepsy reported ASM monotherapy, whereas 27% reported ASM polytherapy.

Table 2
Cardiovascular behaviors, conditions, and examination or laboratory risk factors.

		Mean (SD), median (IQR), and N ^a or Raw no./No. non-missing (weighted %)		p ^b
		Epilepsy		
		Yes (N = 154)	No (N = 17,807)	
Behavior				
Diet	Excellent	12/154 (12%)	1,447/17,803 (8%)	0.03
	Very good	22/154 (12%)	3,533/17,803 (22%)	
	Good	68/154 (48%)	7,215/17,803 (41%)	
	Fair	35/154 (17%)	4,467/17,803 (23%)	
	Poor	17/154 (11%)	1,141/17,803 (6%)	
Minutes of moderate-vigorous work or recreational activity per day	Mean: 86 (SD: 160)Median: 30 (IQR 0–120) N = 152	Mean: 159 (SD: 210)Median: 75 (IQR: 0–240) N = 17,702	<0.01	
Current smoking	40/154 (25%)	3,313/17,794 (18%)	0.06	
Alcoholic drinks/week ^c	Mean: 1.2 (SD: 3.2)Median: 0 (IQR: 0–0.7) N = 84	Mean: 3.3 (SD: 7.7)Median: 0.5 (IQR: 0–3.7) N = 10,524	<0.01	
Condition				
Congestive heart failure		12/136 (12%)	585/16,873 (2%)	<0.01
Coronary heart disease		11/148 (9%)	730/16,849 (4%)	0.03
Diabetes		37/154 (25%)	2,940/17,807 (12%)	<0.01
Hypertension		90/154 (53%)	7,805/17,807 (39%)	0.02
Myocardial infarction		17/148 (10%)	734/16,887 (3%)	<0.01
Stroke		31/147 (21%)	653/16,890 (3%)	<0.01
Examination or laboratory risk factor				
A1c, %		Mean: 5.8% (SD: 1.4%) N = 141	Mean: 5.7% (SD: 0.9%) N = 16,251	0.39
SBP, mm Hg		Mean: 124 (SD: 19) N = 133	Mean: 123 (SD: 17) N = 16,397	0.79
DBP, mm Hg		Mean: 71 (SD: 15) N = 133	Mean: 71 (SD: 12) N = 16,397	0.95
HDL, mm Hg		Mean: 52 (SD: 16) N = 137	Mean: 54 (SD: 17) N = 16,073	0.17
LDL, mg/dL ^d		Mean: 114 (SD: 30) N = 38	Mean: 112 (SD: 35) N = 4,965	0.73
Total cholesterol, mg/dL		Mean: 183 (SD: 35) N = 137	Mean: 190 (SD: 42) N = 16,073	0.09
ASCVD risk, %		Mean: 6.1% (SD: 8.2%)Median: 2.5% (IQR: 0.7%–7.3%) N = 127	Mean: 5.2% (SD: 8.3%)Median: 1.7% (IQR: 0.4%–6.5%) N = 15,493	0.048^b

^a Continuous variables with right-skew are also displayed with median (IQR).

^b p-values were calculated by survey-weighted Chi-squared tests or survey-weighted t-test for difference of means. The except was for ASCVD risk; given substantial right-skew, ASCVD risk was compared via a survey-weighted regression using log (ASCVD) as the outcome.

^c Number of alcoholic drinks per week was calculated as follows. If participants reported <12 drinks/lifetime then they were coded as 0. Otherwise, participants answered how many days they drink per week, month, and/or year, and how many drinks they consumed on a given day of drinking. Number of drinks per day was multiplied by the provided timeframe to calculate average number of drinks per week.

^d LDL sample size was reduced because this laboratory variable was only collected for participants attending the morning session due to the need for a fasting sample.

3.2. Health behaviors, cardiovascular conditions, and physical examination, and laboratory risk factors

The population with epilepsy had worse health behaviors including poorer self-rated diet and less daily moderate-vigorous activity, though fewer weekly alcoholic drinks (Table 2). Although the population with epilepsy reported higher rates of all cardiovascular conditions, there were no significant differences between the two groups in most examination and laboratory risk factors (A1c, blood pressure, and cholesterol). However, participants with epilepsy demonstrated higher aggregate ASCVD risk ($p = 0.048$). Participants with epilepsy had a median 2.5% 10-year ASCVD risk (interquartile range [IQR]: 0.7%–7.3%) compared with participants without epilepsy who had a median 1.7% ASCVD risk (IQR: 0.4%–6.5%). Fig. 1 depicts the distribution for ASCVD risk, along with distributions for SBP, DBP, HDL, and LDL.

Table 3 displays serial regressions regarding the association between epilepsy and log(ASCVD risk). In the unadjusted model (Model 1), participants with epilepsy had a 52% (95% CI: 0%–130%) relative increased ASCVD risk. This relationship was attenuated in adjusted Models 2 and 3.

We then tested whether selected behavioral variables which differed between those with versus without epilepsy mediated

the relationship between epilepsy and increased log(ASCVD risk). Epilepsy did not exert a significant direct effect on log(ASCVD), which was expected given it was nonsignificant in adjusted models in Table 3. Epilepsy did not exert a significant indirect effect through any of the studied variables (Table 4). While most CI demonstrated reasonable precision, the indirect effect of PHQ-9 had an especially wide CI limiting interpretation. While the direct effect of epilepsy had a wide CI, the point estimates for the direct effect of epilepsy on log(ASCVD) (ranging from a 67–76% relative increase in ASCVD) were all greater than the point estimates for any given potential mediator (ranging from –7% to 2%).

3.3. Awareness, treatment, risk factor control, and guideline concordance

Participants with epilepsy demonstrated the same or better rates of awareness, treatment, and control across hypertension, diabetes, and statin use (Table 5). For example, among participants classified as having hypertension, 97% versus 84% of participants with versus without epilepsy reported awareness of their hypertension ($p < 0.01$). Similarly, among participants classified as having hypertension, 83% of participants with epilepsy versus 58% of participants without epilepsy reported treatment for hypertension

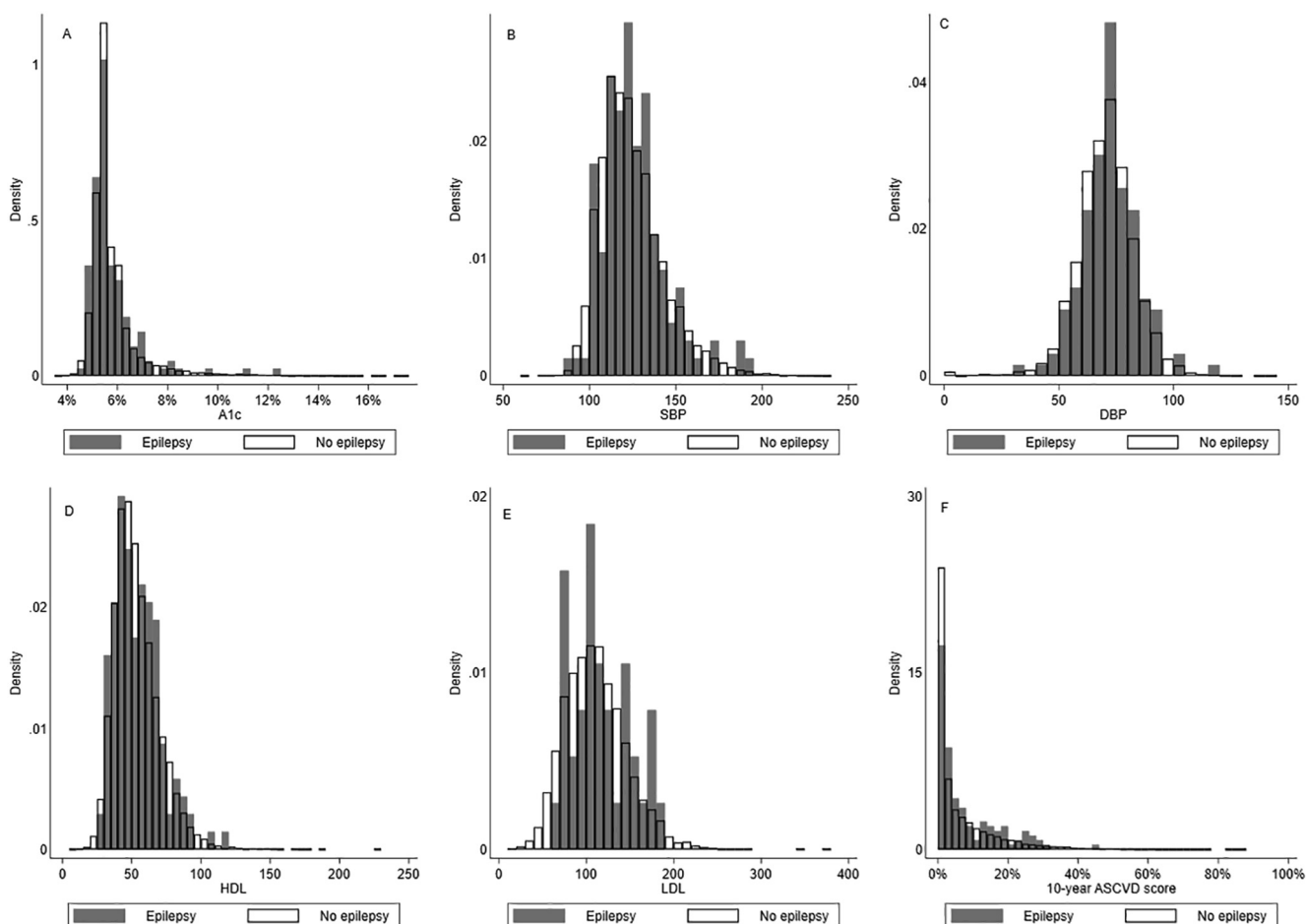


Fig. 1. Distribution of examination and laboratory risk factors stratified by epilepsy: Histograms for the following risk factors with superimposed distributions for people with epilepsy (grey) and people without epilepsy (white). (A) systolic blood pressure [SBP], (B) diastolic blood pressure [DBP], (C) high-density lipoprotein (HDL), (D) low-density lipoprotein [LDL], (E) 10-year atherosclerotic disease [ASCVD] risk. This figure shows that each of the 5 individual risk factors (A–E) was relatively normally distributed other than some right skew, and generally has substantial overlap between the groups with versus without epilepsy. Table 2 lists the p -values from survey-weighted t -tests comparing groups from (A–E) which are all >0.05 . (F) Shows that ASCVD scores were highly right-skewed necessitating our log-transformation when comparing groups ($p = 0.048$). (F) Demonstrates substantial graphical overlap between groups, though the group with epilepsy had scores which were right-shifted compared with the group without epilepsy explaining this significant difference.

Table 3
Predictors of ASCVD risk.

Total N = 17,961		% change in ASCVD risk per 1-unit change in covariate ^a (95% CI)		
		Model 1 N = 15,620	Model 2 N = 13,616	Model 3 ^b N = 13,616
Epilepsy		52% (0–130%)	5% (–22% to 43%)	17% (–6% to 47%)
Diet	Excellent		Reference group	Reference group
	Very good		–17% (–33% to –3%)	2% (–3% to 7%)
	Good		–33% (–43% to –20%)	13% (6–19%)
	Fair		–36% (–47% to –24%)	18% (13–24%)
	Poor		–42% (–54% to –26%)	21% (12–31%)
Hours of moderate-vigorous work or recreational activity per day		–	–4% (–5% to –3%)	0% (0–0%)
Inducer ASM		–	25% (–13% to 79%)	–8% (–28% to 18%)
Body mass index (kg/m ²)		–	4% (3% to 5%)	3% (3–3%)
PHQ-9		–	0% (–1% to 1%)	0% (0–1%)
Stroke		–	15% (5–25%)	16% (6–26%)
Age, per decade		–	–	145% (143–147%)
Male sex		–	–	269% (258–281%)
Non-Hispanic black		–	–	74% (69–80%)
Smoking		–	–	154% (147–161%)

^a Because 10-year ASCVD risk was right-skewed with heteroskedasticity, we used log(10-year ASCVD risk) as the outcome for each linear regression in this table. Interpretation of a logged outcome is therefore a relative percentage change in ASCVD scores for each 1-unit step in covariate, rather than an absolute change in ASCVD risk for each 1-unit step. Each model was adjusted for all variables with a value in the model's column.

^b We reran Model 3 including family income to poverty ratio. Listed coefficients were nearly identical, $N = 12,357$, and the coefficient for income to poverty ratio was -2 (95% CI -3 to -1) suggesting a small correlation between higher income and lower ASCVD.

($p < 0.01$). There was no significant difference in rates of hypertension control. No significant differences were observed for each respective estimate for diabetes. Rates of guideline-concordant statin use were higher for participants with epilepsy (68%) compared to those without epilepsy (45%) ($p < 0.01$). We illustrate these findings in Fig. 2 which displays each outcome and comparison using bar charts with 95% CIs.

Among participants fulfilling blood pressure criteria for hypertension (sensitivity definition), participants with epilepsy were more likely to be aware of their hypertension diagnosis ($p = 0.01$; Supplemental table e-3, left half). Among participants aware of a hypertension diagnosis, rates of control were no different ($p = 0.64$; Supplemental table e-3, right half). No significant differences were observed for either awareness or control using similar denominators for diabetes.

Because awareness may result from counseling following a clinical ASCVD event, we then restricted to those without known cardiovascular disease (coronary heart disease, myocardial infarction, or stroke). Among those with hypertension, participants with epilepsy (48/51; 94%) demonstrated greater hypertension awareness than those without epilepsy (5,293/6,430; 83%) ($p = 0.02$). Among those with diabetes, there was no significant difference in awareness between those with (17/17; 100%) versus without (1,968/2,283; 87%) epilepsy ($p = 0.29$).

We hypothesized that the association between epilepsy and increased hypertension awareness, among those with hypertension, could be mediated by greater outpatient encounters. This is because participants with epilepsy could seek care more frequently for numerous chronic conditions leading to greater chance for hypertension detection and subsequent awareness. As per Table 4, there was a significant direct effect of having epilepsy on hypertension awareness; epilepsy increased the probability of being aware of the diagnosis by 10% or 12%. While there was a significant path from epilepsy to hypertension awareness mediated by having a routine place of care, this indirect effect was small (an absolute 1% increase in hypertension awareness mediated by having a routine place of care) and there was no significant mediation via number of non-urgent health encounters.

4. Discussion

In a large nationally representative sample, we found that participants with epilepsy had similar control of individual examination and laboratory risk factors (blood sugar, blood pressure, cholesterol) compared to participants without epilepsy. However, when risk factors were considered in aggregate, participants with epilepsy carried a 52% relatively high overall cardiovascular risk. This difference was no longer significant after adjusting other patient factors such as health behaviors and demographics. This increase in overall cardiovascular risk was consistent with participants reporting more frequent physician diagnoses across cardiovascular conditions. However, we also found that participants with epilepsy were in general at least as likely as participants without epilepsy to be aware of diabetes and hypertension diagnoses, and were even more likely than participants without epilepsy to receive guideline-concordant statin treatment.

Our initial hypothesis was that participants with epilepsy would demonstrate worse cardiovascular risk profiles (including both worse health behaviors, and worse control of other clinical risk factors) along with poorer awareness of cardiovascular conditions. This hypothesis was informed by several pieces of prior evidence: previous cross-sectional surveys documented 1) increased rates of self-reported diabetes, hypertension, coronary disease, and stroke [12–15], 2) worse health behaviors [21,22], 3) disparities in access to care which could interfere with adequate risk factor control [19], and 4) certain enzyme-inducing antiseizure medications may elevate lipids in people with epilepsy [25]. Our findings partially support these hypotheses. We did find higher self-reported rates of cardiovascular conditions (Table 2), and that participants with epilepsy accordingly demonstrated higher 10-year predicted cardiovascular risk. However, our findings do not support that worse disease awareness or inadequate medical treatment underlies this relationship. In fact, our study found that 1) among participants with hypertension, those with epilepsy demonstrated increased awareness of their condition and higher rates of treatment than those without epilepsy, 2) among participants exceeding blood pressure guidelines, those with epilepsy

Table 4
Mediation analyses.

Potential mediator	Outcome	Pop.	N	Effect from mediation analysis (95% CI) ^a	
				Direct effect of epilepsy on the outcome	Indirect effect of epilepsy on the outcome through the potential mediator
Income to poverty ratio	Log(ASCVD)	All	12,990	76% (-66% to 750%)	-7% (-30% to 11%)
PHQ-9	Log(ASCVD)	All	12,990	76% (-66% to 750%)	2% (-92% to 938%)
Diet ^c	Log(ASCVD)	All	12,990	67% (-65% to 812%)	0% (-4% to 5%)
Smoking	Log(ASCVD)	All	12,990	76% (-66% to 750%)	2% (-10% to 28%)
Number of non-urgent health encounters	Hypertension awareness	Participants with hypertension	7873	+10% (+3% to +20%)	+1% (-18% to 10%)
Having a routine place of care	Hypertension awareness	Participants with hypertension	7873	+12% (+6% to +16%)	1% (0% to +1%)

^bThe direct effect is the predicted increase in the outcome due to having epilepsy. The indirect effect is the predicted increase in the outcome due to having epilepsy, as a result of epilepsy’s influence increasing the potential mediator which in turn influences the outcome. When outcome was log(ASCVD), the effect is $(e^{\text{coefficient}} - 1) * 100\%$ to calculate the relative increase in ASCVD related to having epilepsy (direct effect), or the relative increase in ASCVD related to having epilepsy as a result of possible mediation through the variable in the listed row (indirect effect). When the outcome was hypertension awareness, the effect is the expected change in absolute probability of hypertension awareness related to having epilepsy (direct) or related to mediation by the variable listed in each row (indirect). Each model was adjusted for initially hypothesized possible mediators: income to poverty ratio, PHQ-9, being on an inducer, diet, hours of moderate-vigorous activity per day, smoking.

^a We performed models to assess the degree to which the relationship between epilepsy and two different outcomes (1) log(ASCVD), and 2) hypertension awareness) was mediated by a variety of potential mediators. We initially hypothesized income, depression, enzyme inducer, diet, exercise, and smoking could mediate the relationship between epilepsy and ASCVD risk. Unadjusted analyses where epilepsy predicted each potential mediator revealed significance ≤ 0.01 for income, PHQ-9, inducer, diet, and exercise). Epilepsy predicted smoking with $p = 0.06$. We thus selected those variables which were also significant in Table 3’s fully adjusted Model 4 for consideration as possible mediators (income, PHQ-9, diet, smoking; enzyme-inducing medication and exercise were not possible mediators given their non-significance in Model 4). We then also assessed whether several variables capturing outpatient care (number of non-urgent healthcare encounters, having a routine place of care) mediated the relationship between epilepsy and greater hypertension awareness.

^c Diet was entered as a binary variable (at least good diet versus fair/poor).

Table 5
Awareness, treatment, control.

	Awareness ^a			Treatment			Control ^b		
	Epilepsy		<i>p</i> ^c	Epilepsy		<i>p</i>	Epilepsy		<i>p</i> ^c
	Yes	No		Yes	No		Yes	No	
Hypertension	87/90 (97%)	6,583/7,800 (84%)	<0.01	73/89 (84%)	4,736/7,606 (59%)	<0.01	57/90 (65%)	3,920/7,805 (54%)	0.11
Diabetes	34/37 (83%)	2,582/2,939 (89%)	0.43	27/37 (71%)	1,846/2,940 (61%)	0.34	25/37 (57%)	1,556/2,940 (54%)	0.80
Statin ^d	N/A	N/A	N/A	36/64 (68%)	2,299/5,234 (45%)	<0.01	N/A	N/A	N/A

^a Awareness: numerator/denominator = (Reporting a physician had diagnosed the condition or taking a medication for that condition)/(Participants classified as having the condition). Participants were classified as having the condition if they reported a physician had diagnosed the condition, reported taking a medication for that condition, or exceeded examination or laboratory threshold for the condition. Examination or laboratory thresholds were SBP ≥ 140 (≥ 130 if diabetes) or DBP ≥ 90 (≥ 80 if diabetes) for hypertension, or A1c $\geq 6.5\%$ for diabetes.

^b Control: numerator/denominator = (Examination or laboratory measurements below control thresholds)/(Participants classified as having the condition). Control thresholds included SBP < 140 (< 130 if diabetes) and DBP < 90 (< 80 if diabetes) for hypertension, and A1c $< 7\%$ for diabetes.

^c *p*-values are all from unadjusted survey-weighted chi-squared tests.

^d Statin treatment: numerator/denominator = (Reporting taking a statin)/(Participants for whom guidelines recommend a statin). Guidelines recommend a statin if clinical ASCVD (self-reported myocardial infarction, angina, or stroke), diabetes and age 40–75, 10-year ASCVD risk $\geq 7.5\%$, or LDL ≥ 190 mg/dL).

were more likely to be aware of their diagnosis, and 3) among participants with an indication for a statin, those with epilepsy demonstrated higher rates of statin treatment compared with those without epilepsy. While we initially hypothesized that increased disease awareness could be mediated by increased healthcare encounters, our mediation analysis did not confirm this hypothesis, and thus it is possible that other factors which we did not capture (e.g. intensity or specialization of care at a given visit, or patient attentiveness to health given numerous chronic conditions) could mediate this relationship. Thus, increased healthcare contact alone did not explain the higher disease awareness, and also was not enough to overcome worse raw ASCVD scores in people with epilepsy.

Our analyses emphasize the central importance of lifestyle modification and influence of nonmodifiable factors, rather than a medical treatment gap regarding blood pressure or any particular laboratory metric. In our study, the nonmodifiable effect of age (approximately 140–150% relative increase in ASCVD per decade) dwarfed the effect of epilepsy (approximately 20–30% relative increase adjusted for demographics). However, other modifiable factors related to health behaviors such as diet, exercise, and smoking were all significantly related to ASCVD risk, even if not signifi-

cant mediators along the pathway from epilepsy to ASCVD risk. In particular, current smoking was substantially more strongly correlated with ASCVD risk (109–155% relative increase in ASCVD in serial models) than epilepsy itself (26–58%). This is unsurprising given smoking is one variable included in ASCVD risk calculation, and important in the context of prior literature showing increased rates of smoking in patients with epilepsy [20]. Poor diet, which is not included in ASCVD calculation, was also associated with an independent 17–21% relative increase in ASCVD scores in participants with epilepsy and participants with epilepsy reported worse diet than those without epilepsy.

Our study has several limitations. First, certain variables had measurement limitations. Our inclusion criteria based on available data (taking ≥ 1 ASM for seizures or epilepsy) may not have captured all participants with epilepsy; participants with well-controlled epilepsy may eventually appropriately discontinue their ASM [42], or else participants may inappropriately not receive an ASM despite it being indicated (the “treatment gap”) [43]. However, we believe this is a reasonable definition because identification of epilepsy by self-report has been validated with positive predictive value of 74% and sensitivity of 84% [44], presence of an ASM has been shown to substantially improve detection of epi-

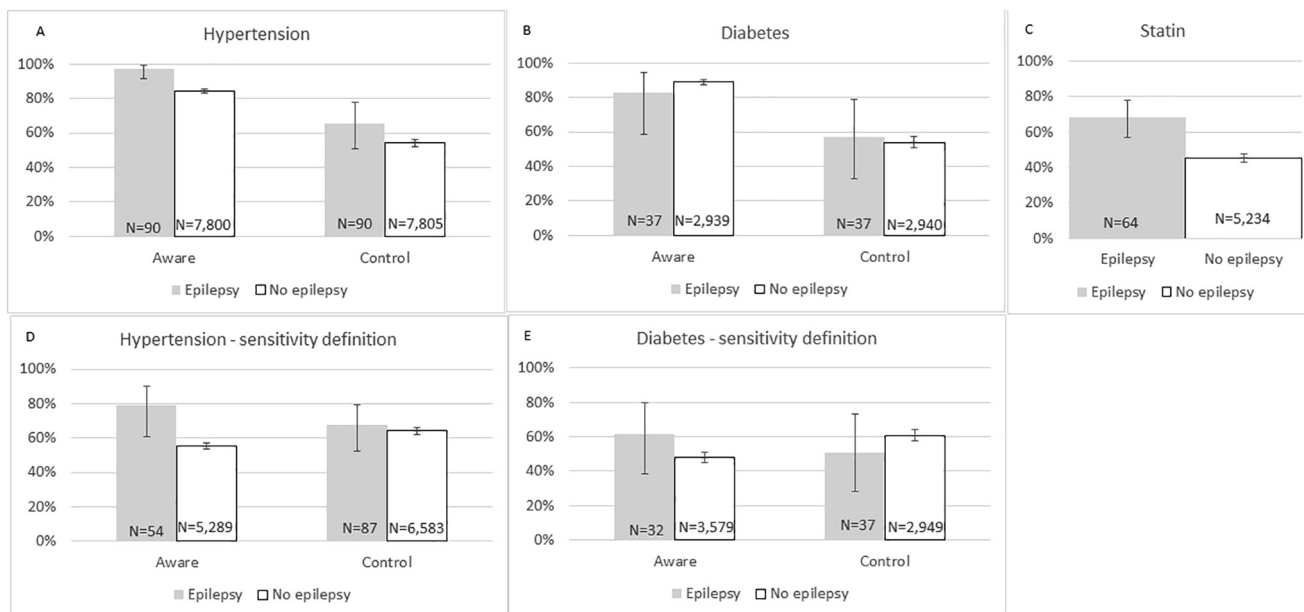


Fig. 2. Awareness, treatment, control: This figure graphically presents information contained within Table 5. See footnotes in Table 5 for descriptions of variables. The figure displays 95% confidence intervals around each proportion in addition to each group's sample size.

lepsy in research datasets [45], and ASMs are the mainstay of treatment for epilepsy. Other self-reported variables could be measured with error too; for example, self-reported physical activity has been shown to overestimate physical activity compared with accelerometry [30]. However, we have no reason to suspect measurement error differed between our groups, so this is unlikely to have biased our comparison. Also, NHANES does not contain information regarding epilepsy characteristics such as disease duration or seizure frequency, severity, or refractoriness (other than number of ASMs) which could more fully describe our population with epilepsy. Still, because of the dataset's national representativeness and essentially absence of selection bias due to rigorous population sampling methods across 6 years of data, our population with epilepsy's seizure characteristics are expected to unbiasedly reflect those of the US population with epilepsy. Additionally, the dataset contains excellent assessment of confounders which could possibly influence our main outcome (ASCVD risk), for example objectively measuring body mass index, lipids, blood pressure, A1c, etc. Despite some variables being self-reported, NHANES provides exceptionally detailed information regarding other confounders (smoking, exercise, diet, cardiovascular conditions, enzyme-inducing antiepileptic medications, etc.) which otherwise would have distorted our main comparison had the dataset been rich in seizure characteristics but lacking in cardiovascular variables.

Second, our modest sample size of 154 participants with epilepsy could have limited power. However, our results suggest non-significance of epilepsy in Models 2 and 3 for example could have simply been due to true effect attenuation after adjusting for our wide range of cardiovascular-related covariates. Model 1's relative effect was 52%, whereas Model 2 and 3's relative effects were 5% and 17%, respectively, which supports that there is a meaningful unadjusted relationship, but that when considered simultaneously the other listed associated factors are more likely to drive ASCVD scores rather than epilepsy itself. Also, power was boosted by a large sample without epilepsy (N = 17,807) and ASCVD being continuous rather than binary. To illustrate this, given the mean ASCVD risk for the non-epilepsy group was 5.2%, Model 3 (where the 95% CI around the relative effect of epilepsy was -6% to +47%) would suggest CI bands for someone with epi-

lepsy of $5.2\% \times (1 - 0.06) = 4.9\%$, to $5.2\% \times (1.47) = 7.6\%$, which is a reasonably precise estimate. Our sample size was adequately powered to detect an unadjusted effect of epilepsy on ASCVD, in addition to, for example, difference in hypertension and statin-related parameters between groups. Nonetheless, power was likely lower for binary comparisons with smaller sample sizes (i.e. diabetes awareness, treatment, and control) or certain parameters in our multi-regression mediation analyses as made transparent by listed CI. To more fully elucidate the causal pathway, a larger sample size of patients with epilepsy would be beneficial in future work.

Third, the cross-sectional study design measures associations but does not determine causation. The dataset does not inform whether participants developed cardiovascular risk factors before or after developing epilepsy.

While we are not aware of any other existing dataset with equally high-quality capture of ASCVD-related variables in an unselected nationally representative population, future work aimed at further understanding the influence of epilepsy characteristics (i.e. chronicity and severity) on health behaviors and ASCVD especially with a larger sample size of patients with epilepsy would be valuable.

5. Conclusions

Participants with epilepsy reported higher rates of cardiovascular diagnoses. Despite similar control of individual cardiovascular examination or laboratory risk factors, similar or better risk factor awareness, and greater frequency of healthcare encounters, participants with epilepsy nonetheless demonstrated 52% higher 10-year predicted cardiovascular risk compared to participants without epilepsy. This association was attenuated after accounting for health behaviors, and numerous health behaviors significantly influenced cardiovascular risk after adjusting for epilepsy even if they did not mediate the relationship between epilepsy and risk. Our work only establishes association rather than causation, given the cross-sectional data without ability to determine whether epilepsy or cardiovascular disease arose first. Our work nonetheless suggests that to close the gap in cardiovascular risk, clinicians

could increase interventions targeting health behaviors associated with risk (rather than cardiovascular pharmacologic treatment gaps), interventions may need to focus on content of a given encounter rather than simply frequency of encounters, and future studies clarifying this complex causal pathway are warranted to better understand the likely multifactorial driving mechanisms. Nonetheless, this is not to diminish the importance of continued efforts intending to improve approaches to seizure-related treatment or treatment of drug-resistant epilepsy, as it is well-recognized that a pharmacologic treatment gap exists whereby many patients unfortunately receive under- or delayed treatment of seizures [43,46].

Author contributions

Dr. Terman contributed to hypothesis generation, study design, data collection, statistical analysis, and manuscript preparation. All other authors contributed to study design and manuscript preparation and editing.

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Declaration of interests

None.

This work has not been published previously and is not under consideration for publication elsewhere. This work contains similar populations as two recently accepted manuscripts (Epilepsy Behav. 2020 Sep 9;112:107429; Epilepsy Behav. 2020 Jul 3;111:10726), but the current manuscript presents unique analyses to answer distinct research questions from the prior manuscript and thus does not overlap. This publication is approved by all authors, by the responsible authorities where the work was carried out, and if accepted will not be published elsewhere in the same form without the written consent of the copyright holder.

Declaration of competing interests

The authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2021.107878>.

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